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with the author's kind regards

ON THE
ACTION AND USE
OF THE
OPIUM ALKALOIDS CRYPTOPIA AND
THEBAIA.

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CRYPTOPIA.

THE only observations on the physiological action of this alkaloid are those made by myself three or four years ago, and recorded in my work on 'The Old Vegetable Neurotics.'

A very limited supply of the substance prevented me at that time from extending my observations as far as I wished, but the renewed kindness and liberality of Messrs. T. and H. Smith, of Edinburgh, the discoverers of the alkaloid, have enabled me to advance them a step or two further.

The chemical characters of the alkaloid used in the following observations are those of the pure substance described at p. 165 of my work. It is there stated, on the authority of Messrs. Smith, that it exists in opium in the proportion of about one ounce to a ton; but these gentlemen have since informed me that they have succeeded in isolating it in double this proportion, and that there are grounds for inferring that a ton of opium contains at least four ounces of cryptopia, the percentage being probably equal to that of meconine, viz. 0.026. In the following observations, a solution of the alkaloid in water containing a slight excess of acetic acid was employed: 100 minims of the solution containing five grains of the pure alkaloid.

PHYSIOLOGICAL ACTION.—This has been studied afresh on the dog, the cat, the rabbit, and on man.

ON THE DOG.—The effects of cryptopia on the dog vary like those of morphia, but not to the same extent, for they are always eminently characteristic. In one class of this animal—that in which morphia causes persistent nausea, faintness, and restlessness—cryptopia produces a most remarkable excitement of the voluntary movements, followed by somnolency. In the other class, that in which the hypnotic effect of morphia is readily induced to the exclusion of any notable derangement of the vagus, cryptopia still manifests its peculiar action, but the hypnotic and convellent effects are more equally balanced, and in some animals the former effect exceeds the latter and partially effaces it. Thus:

Obs. 1.—Injected beneath the skin of a young dog weighing twenty-one pounds, and in whom the subcutaneous use of half a grain of morphia induced complete narcotism for eight hours, one and a half grain of cryptopia. The operation frightened the dog, and after ten minutes he was dull and slobbered very much, clear glairy mucus dropping occasionally from his closed mouth. After thirty minutes, the first stage of excitement, the seemingly prying motions of the head were observable, but these soon subsided, and he lay down at my feet and remained very quiet during the next hour. Pulse 120 and regular, the pupils dilated, and clear mucus dropping continually from the mouth. He seemed in a dozy, dreamy condition. When disturbed at the end of the second hour, he followed me down stairs; ate food as usual at the third hour, and then lay down and slept tranquilly for several hours.

The effects of the same dose on a dog of the other class mainly consist in extraordinary vivacity of mind and body, marked by an interesting play of voluntary and involuntary movements. This condition is fully described in my work, and it is well illustrated in the following observations on the cat and rabbit, whence it will appear that the action of cryptopia on the dog, cat, and rabbit, and so far on carnivora and herbivora, is remarkably uniform.

ON THE CAT.—*Obs. 2.*—Injected half a grain of eryptopia beneath the skin of a young cat, A, weighing two pounds. After eighteen minutes she began to look about intently in front of the nose. After twenty minutes, pupils dilated; mouth and throat

uncomfortable, evidenced by licking the lips, and efforts of swallowing; walked slowly and naturally, looking pryingly about her. After thirty-five minutes, champing and swallowing, slobbering of tenacious mucus. After forty-five minutes, advanced very slowly, apparently impelled forwards, and yet holding back and moving with hesitating advance of the fore paw and frightened looks, only a step in a minute, as if she were walking on dangerous ground. This continued until the end of the second hour, when the pulse was 240, the pupils still dilated. Apparently about to advance, the body was swayed backwards and forwards, as she looked with a scared aspect from side to side, as if under the influence of some illusion; and thus she succeeded about once in ten minutes in advancing a pace forwards. At the fourth hour the slobbering had ceased, and she mewed in recognition of my call. Pulse 200; pupils contracting a little at the light. Half an hour afterwards she had quite recovered.

The experiment was repeated with another cat of the same age and family with exactly the same results, viz. slobbering of tenacious mucus; forward impulsive movements; dilated pupils. Heart beats from 260 to 280; respiration accelerated 80.

Obs. 3.—Injected three quarters of a grain cryptopia beneath the skin of a young cat weighing about three pounds. After five minutes, she suddenly started across the room in an awkward frightened manner, and began to lick the lips, and then became quiet. After fifteen minutes, characteristic effects came on and continued for the next three quarters of an hour; the fore legs were advanced, a little outspread and firmly set, and the head retracted and affected with rapid jerking movements backwards and forwards and from side to side. Now and then a fore paw was raised from the ground and twisted or shaken with spasm, and then the body while rigidly oscillating, as it seemed, between a forward and backward impulse, was thrown forwards in a nervous scramble. After a succession of such movements the animal got into a corner, and there continued to jerk the head about as if constantly avoiding a prick of the nose. When approached, she manifested first great nervousness, then anger, putting back her head and hissing at me, but after a little caressing she became more composed and seemed comforted; the choracic movements of the head and fore paws continued; the

respiratory movements were increased, and the pupils dilated to twice their initial size. Brought again into the centre of the room, she got back into the corner by a succession of the hesitating scrambling movements, the body being arrested as soon as the rush was made, by the rigid forward set of the fore legs. These spasmodic movements gradually declined, and ceased about an hour and a half after the injection, and the animal remained in the same corner during the next ten hours sleeping comfortably. At the end of this time she had taken neither food nor water, nor passed any excretions. Next day she was quite well and lively.

Obs. 4.—Injected one grain cryptopia beneath the skin of a young cat of the same family, age, and weight as A. She continued quiet, but, after ten minutes, strings of frothy tenacious mucus were hanging from the mouth, and she began looking attentively from side to side. After fifteen minutes, these symptoms continuing, the tail was extended, and curved upwards near the root; the body rigid and tremulous, apparently impelled forwards, and the impulse resisted or balanced by a rigid advance and set of the forelegs. While in this attitude a fore paw was occasionally raised slowly and supinated, and then advanced as if striking at a mouse. When the animal had maintained this constrained attitude for two minutes, she was suddenly hurled forwards, and rolled over and over in an opisthotonous convulsion, which lasted half a minute. As soon as the animal regained her legs she was impelled forwards in a succession of little convulsive leaps, first to the right and then to the left, the tail and ears erect, and the head rapidly jerked from side to side, the pupils dilated and the eyes staring. As, however, she constantly regained her legs, she seemed to be wildly scampering after a mouse. After twenty-two minutes she crept slowly and quietly along, with a stiff, awkward timid gait—the extended tail and erect ears being occasionally strongly twitched; mewling and answering when spoken to—and couched. While in this position, all the muscles were affected with intermittent spasm; now a hip was suddenly raised, nearly throwing the animal on her side; now the muscles along the back of the neck were violently worked; and now a fore arm was raised, the claws extended, and the limb shaken with spasm; one or other ear meanwhile was in a state of vibration. This continued to increase until the thirtieth minute, when she was thrown forwards

a second time, in a most violent tetanic spasm. It lasted but a second, and as the cat lay on the side the suspended respiration was re-established with slow and laboured inspirations, until they increased to seventy, and became regular; then the animal was for a few minutes free from spasm, and continued lying on her side looking about intelligently. At the fortieth minute the twitchings came on again, and the cat, having raised herself on the slightly-sprawling and floor-clutching legs, was alternately swayed backwards and forwards until the forty-seventh minute, when she was again thrown violently forwards in a third convulsion, in which all four legs were affected with most rapid movements. The attack lasted about fifteen seconds, and the breathing was recovered as before. The cat now seemed recovered, but exhausted, and she moved a length now and then when disturbed. At the fifty-second minute the spasm returned, in a milder degree; and at the fifty-fifth minute the body was raised on the haunches, the head and chest being curved forwards, and the fore paws incurved, and shaken for a few seconds with the most violent and rigid spasm. This over, the cat fell exhausted on her side, relaxed and apparently dead; the breathing, however, was restored by one or two laboured inspirations. At the sixtieth and sixty-second minutes, she had a fourth and fifth convulsion, the former lasting twenty seconds; in the interim the respirations were twenty, snatching and irregular. After the last attack she lay on her side breathing freely and deeply; but shortly afterwards she regained the couching position, with her fore legs a little sprawling, and, while in this position, and from this time up to the end of the fourth hour, the body was affected with constant choreic movements. These were at first so severe that the animal could not stand, and, as she lay along on the belly, the writhings of the muscles of the trunk moved the body half a circle from left to right in the course of half an hour. The abdominal muscles were strongly worked, and the head was extended and twisted in a wriggling manner by the spasm of the cervical muscles. The pupils were widely dilated throughout. During the earlier part of the choreic stage the respiration was twenty, irregular; the inspiration labored, and the expiration short and explosive; the heart's action weak and rapid. Towards the decline of the chorea the respiration increased to eighty, but continued

irregular ; heart beats 260 and regular. The intelligence was apparently unimpaired throughout. From the fourth to the eighth hour the animal remained in a quiet dozy state, but passed no excretions from first to last. Next day she had quite recovered.

The effects of morphia on this animal in doses varying from $\frac{3}{10}$ ths to $\frac{1}{2}$ grain, were delirium and restlessness with increased cardiac action and temperature, and complete and fixed dilatation of the pupils. Effects in fact precisely similar to those which follow the use of morphia in the horse.

ON THE RABBIT.—*Obs. 5.*—Injected two grains of erytopia beneath the skin of an adult male rabbit, A. Immediately afterwards the respiration was 160 and panting, apparently from the excitement caused by the act of injection. He continued to hop and pry about the room actively and naturally until the seventh minute, when he erected an ear, and began to pant, and to hop round at short intervals. During the next few minutes the excitement increased ; and, as he hopped sideways in a circle, the head was constantly advanced, and the nose rapidly worked with a sniffing motion, as if the animal was busy upon some object before its face. A fore paw was occasionally advanced as a preliminary to the hopping movement ; the chest was contracted, and in vibration from rapid panting. After fifteen minutes, he began to slip forwards a little on the legs, the fore limbs being extended forwards, and seemingly exerted to prevent the advance. After half an hour, having continued in the same state, the head was now raised, and jerked backwards and forwards, the lips being separated each time the head was jerked backwards, and the animal was suddenly advanced a pace, as often the apparently voluntary resistance gave way to the involuntary impulse forwards ; pupils widely dilated ; respiration still a fine pant. After three quarters of an hour, the hind legs seemed weak, and the forward movement was more clumsily restrained. After one hour, heart beats 160 ; respiration still shallow and panting ; pupils still dilated ; restlessness decreased. From this time the symptoms slowly subsided, and after five hours from the injection, the animal leisurely ate a little green stuff. After six and a half hours he was in his usual condition, but as yet had not passed any excreta.

Obs. 6.—Injected, by four punctures, three and a quarter grains of cryptopia beneath the skin of another adult male rabbit, B. After fifteen minutes he was in the state of rabbit A (*Obs. 5*), at the same time. After twenty minutes the hind legs gave way, and the animal lay on the chest and belly, the head being rapidly jerked backwards and forwards, and from side to side. Occasionally the head was bent downwards, and the nose frequently tapped on the floor. After twenty-five minutes, lost the use of the fore legs; occasional spasm in the hind legs, slightly advancing the body; increased restlessness of the head; respiration 80, short, snatching, and somewhat irregular; pupils a little dilated. After thirty minutes, the jerkings and writhings of the head and neck increased, with very strong retractile action of the muscles of the neck, while the facial muscles, and especially those of the lips and vibrissæ, were powerfully convulsed. Five minutes later the muscles of the lower jaw were similarly implicated, the mouth being alternately opened and closed, with strong grinding of the teeth. The tongue was also convulsed. The animal now lay on the side, incapable of voluntary movement, the hind legs and hips flaccid, and the muscles of the face, head (excepting the orbicularis and muscles of the eyeball), chest, shoulders, and fore legs in a constant state of regularly intermittent spasm, the twitchings numbering fifty in the minute, and being synchronous with the inspirations. Heart's action meanwhile quite regular, and 140. The parts unaffected by spasm were not paralysed, for the hind leg was drawn up when touched, and the eyelids closed on attempting to approach the cornea. After one hour, the eyelids and hind legs were affected with spasmodic twitchings. Pupils of their initial dimension. The animal continued in this state until the end of the second hour, when the twitchings began to intermit, and give place to intervals of quiet of a few seconds duration. It had lately been impossible to count two successive inspirations, or even to distinguish the respiratory movements from the general twitchings of the muscles, but now five or six panting inspirations could be counted continuously. There was no apparent change in the circulation, and the body continued very warm. After two and a quarter hours the animal struggled to get on the belly, but was unable to retain this position until seven minutes later on, when he had just power

enough to maintain the couching posture. Heart beats 160; respiration 144, irregular, being sometimes accelerated to a quicker pant. The head alone was restless now.

From this time the symptoms rapidly passed off, and at the fifth hour the animal seemed to have quite recovered. Up to the seventh hour no excretions were passed.

Obs. 7.—Injected three and a half grains of cryptopia into the subcutaneous tissue of rabbit A. After forty minutes, one grain more, and one hour later another grain, making in all five and a half grains. Up to the forty-fifth minute the effects were precisely the same as those described in *Obs. 5*, the head being constantly twitched, the hind legs weakened and still, and the body slowly moved round in a circle from right to left by the spasms of the anterior part; the chest contracted, and the respiration reduced to a fine, rigid, irregular panting, numbering 160 a minute. During the second hour the symptoms were the same as those in *Obs. 6*, at that period of the operation of the drug; there was the same powerful grinding of the teeth and writhing of the tongue. The muscles of the eyeball and the orbicularis muscle escaped throughout, and the latter exhibited reflex movement up to the time of death. Half an hour after the third injection, the muscles of the face, neck, shoulders, and upper part of the chest were still affected with incessant twitchings, but the spasms were growing weaker, and the rest of the body was flaccid, and losing heat. Four hours after the first injection the spasmodic movements had become very weak, but not less frequent, and being now confined to the shoulders, neck, and head, the respirations could be counted; they were 50, and very faint; the heart beats 96, and feeble; the pupils dilated. The spasmodic movements became gradually weaker, until at last they were almost imperceptible, and then the animal was dead; this occurred four hours and twenty minutes after the first injection. At the moment of death the pupils contracted to their initial size, and the temperature of the rectum was 94° Fahr.

The body was opened ten minutes after death; the diaphragm was drawn up into the chest; the lungs collapsed, pale, and crepitant; the large veins at the roots full of dark blood. Both auricles were contracting synchronously and regularly 70. Shortly after the pericardium was opened, the ventricles began

to contract, and continued to do so regularly sixty times a minute.

The ventricular contractions chiefly affected the apex of the heart, the left side of the organ being twisted forwards to the right, and the apex at the same time drawn upwards towards the base, and flattened. These movements continued for fifteen minutes after opening the pericardium, and were independent of the withdrawal of blood from the heart. All four cavities of the heart, the pulmonary veins, and their branches in the lungs, as well as the *venæ cavæ*, were distended with dark venous blood, and it was clotted in the ventricles. The urinary bladder was full, and the stomach and intestines were filled with food and *fæces*.

ON MAN.—The main conclusions which, from a limited number of observations, I formed three years ago as to the action of cryptopia on man, were as follows:—1. The hypnotic effect is both considerable and protracted in those who are readily calmed by morphia, and that in this respect it is one fourth as powerful as morphia. 2. Although no unpleasant effects have followed its use in man, further experience is required to show that, as a hypnotic, it possesses any advantage over morphia.

Subsequent experience has confirmed me in the former of these conclusions, and with regard to the latter I am able to say that, as a gentle hypnotic, used subcutaneously, it does possess considerable advantages over morphia. In only one case has the subcutaneous use of the drug been attended by any unpleasant consequences, but even this does not properly form an exception. I give the case with the patient's statement, in order that my readers may form their own opinion. The other cases will serve to illustrate the general and particular effects of the drug.

Obs. 8.—James B—, æt. 55, a feeble, anæmic man, afflicted with general rheumatic neuralgia. Pulse 90, regular, of fair volume and power. Right pupil one eighth, left one ninth. Injected ℞xxiiss of solution of acetate= $1\frac{1}{2}$ grain of cryptopia, beneath the skin of the arm. After seventeen minutes, pulse 76, pupils unchanged; somnolency, but felt faint. After twenty-seven minutes, continued feeling of faintness, cold and pale; pulse 60, weak, regular. Gave him ʒj Spir. Ammon. co. in a draught of

water. Still sat quietly in the chair, and moaned occasionally when left alone. The faint feeling gradually passed off. After three quarters of an hour, pulse 60, weak and regular; respiration 30, regular; pupils unchanged; tongue natural; surface cold. After two hours, quite comfortable and dozing; pulse 58, regular, of initial volume and power; respiration 20; pupils unchanged; continued to doze comfortably for another hour and then walked home. I attributed the faintness to the action of the medicine, but the patient assured me it had nothing to do with it as he was liable to frequent attacks of the kind, and that they were occasionally of greater severity than the one I had witnessed. A week after, he reported himself as being free from pain.

Obs. 9.—Thomas W—, æt. 31, a strong man affected with right facial neuralgia. Pulse 88, tongue moist; pupils, the right $\frac{1}{7}$ th, the left $\frac{1}{6}$ th.¹ Injected into the subcutaneous tissue of the arm ℞xxiiss of solution of acetate = $1\frac{1}{2}$ grain cryptopia. After twenty minutes, decided dilatation of the pupils, and somnolency. After thirty minutes, pulse 84, tongue unchanged; pupils, right one sixth, left one fifth; considerable somnolency. Went home and slept soundly for some hours. After a week he reported that the tic passed off under the influence of the cryptopia, and had not reappeared. This was five weeks ago, and as he has not reappeared amongst my out-patients I conclude that the relief has been thus far permanent.

Obs. 10.—Charles H—, æt. 18. Insomnia, fifth day of typhus. Pulse 100; respiration 24; pupils one seventh; tongue clean, dry, and glazed. Injected solution of acetate = to $1\frac{1}{2}$ grain cryptopia, into the subcutaneous tissue of the arm. After twenty minutes, pulse 96; respiration 26; pupils and tongue unchanged; inclined for sleep. After one hour and a half, had slept comfortably since last seen. Pulse 96, increased in volume and power; respiration, sleeping 36, waking 30. Pupils dilated as he slept, on waking, one fourth; felt quite comfortable. After two hours, was still sleeping; pulse 96; respiration, sleeping 40, awake 36. After three hours, still sleeping; respiration 40 sleeping, awake 36; pulse 100. Five hours after the injection, passed f3xvj of dark brownish acid urine like maltwort, sp. gr. 1027·2; on standing it deposited a quarter of its volume of stone-coloured fluffy amorphous deposit, soluble in ammonia. The clear urine had

¹ See *Obs. 15, et seq.*

a peculiar glaucous-brown colour; it contained a large excess of lithic acid.

After an interval of three days the injection of $1\frac{1}{2}$ grain cryptopia was repeated, the pulse being 100, respiration 36, and the pupils one seventh. After thirty-five minutes, pulse 98, respiration 36, pupils one sixth; a troublesome cough had prevented sleep. After one hour, pulse 100, respiration 40; sweating moderately, and was comfortable and inclined for sleep. After two and a quarter hours, slept since last seen; pulse 100, respiration 40, pupils one sixth. Five hours after the injection, passed $f\bar{3}vij$ of normally acid urine, sp. gr. 1022, of the same peculiarly yellowish- or greenish-brown colour, quite bright and free from deposits.

Obs. 11.—Injected solution of the acetate in doses varying from 1 to $1\frac{1}{2}$ grains, beneath the skin of a weakly man of middle age who had suffered long and severely from sciatica. The anodyne effect of the drug was immediate, marked, and enduring. As a hypnotic the result of its action was most satisfactory. Somnolency came on about ten minutes after the injection and continued for five or six hours; the sleep was tranquil and undisturbed by dreams. Dilatation of the pupil was a marked effect in this case.

ELIMINATION.—The urine excreted after the action of cryptopia, in the cases in which I have had an opportunity of examining it, has possessed a peculiar yellowish- or greenish-brown tinge by transmitted light. This was the condition in *Obs.* 7 and 10. On opening the bladder of the rabbit I found the urine crowded with white pyriform bodies, about half the size of a grain of wheat, and of faint outline and gelatinous appearance, but quite distinct and of equal size. Searching as I was for *Bilharzia* (having fed the animal on the eggs of the parasite), my first thought was that they might be a brood of minute flukes. This idea, however, was not long tenable, and my second conjecture, remembering the remarkable way in which narceine is separated from the blood in the kidney, was that the bodies were jelly-like masses of cryptopia, as they had been dropped from the orifices of the tubules into the calyces of the kidney. This led me to examine the urine for cryptopia. I collected a portion of the jelly-like bodies on a filter, and washed them free from urine, and, having dried the filter, boiled it in absolute alcohol to abstract any cryptopia. The hot alcohol

filtrate was allowed to evaporate spontaneously in a watch-glass. A stain remained, composed at the margin of a few minute scattered prisms. On causing sulphuric acid to flow over the stain, a rich violet colour was developed, and on heating the fluid it became slate coloured, thick, and opaque. The other portion of urine was treated, first with acetic acid, which dissolved the gelatinous bodies, and then with ammonia to neutralization. The deposit thus obtained, composed chiefly of phosphates, was washed and exhausted with alcohol. The stain left by evaporation also gave a violet colour. Hence I think it may be inferred that a minute quantity of cryptopia was present in the urine; but the jelly-like masses could scarcely have been wholly composed of this substance, for in this case the quantity obtained would have been greater; probably they were formed by the deposit of phosphates, in the most delicate gelatinous film of cryptopia. I examined the urines obtained in Obs. 10 in a similar way, and, by means of hot chloroform, obtained from the deposit of washed phosphates a filmy residue; but this developed only a reddish-brown colour with sulphuric acid, becoming darker on the application of heat.

CONCLUSIONS.—Taking now a general review of the action of cryptopia, we cannot fail to see that in its effects on the nervous system it stands exactly midway between morphia and thebaia, sharing equally in the qualities of both. We have applied the test of different nervous systems to the substance, and found that those of the mouse, of some dogs, and of man, give sleep, while those of other dogs, of the cat, and of the rabbit, give convulsion. A grand physiological truth lies here, for surely these experiments teach us that sleep and convulsion are but one, mutually and readily interchangeable, the variation being determined by certain peculiarities resulting from mechanical or molecular variations of the nervous system; in a word, the one test gives us white light, the other a coloured spectrum.

He must be a dull observer of disease who has failed to recognise the close relationship of sleep and convulsion. How many an epileptic patient, for example, is distressed with the thought that, on laying himself down to rest for the night, sleep and convulsion will struggle for the possession of his nervous system, or that, on rising in the morning, and before he has

completely shaken off the influence of sleep, convulsion may assert its relationship !

After witnessing the extreme susceptibility of the mouse to the tetanizing action of thebaia and codeia, and seeing a powerful dog thrown over and over in the convulsions produced by cryptopia, nothing has surprised me more than to see the former little animal sleeping soundly for many hours under the influence of a moderate dose of cryptopia, and passing, under the action of a larger, from the state of narcotism to that of death, without the slightest movement.

What is the explanation of this apparent anomaly ? Are the nervous systems of the different physiological classes of animals like different musical chords ? and do the constituents of opium correspond to variations of a particular note, one of which is in unison with this particular chord, another with that, while all the rest are more or less at variance with both ?

But, to return to facts, we have yet to discriminate a difference in the hypnotic action of cryptopia and morphia on the one hand, and a difference of excitant action between cryptopia and thebaia on the other. First as to the excitant action, the broad distinction between the two alkaloids is this—that the convulsion of thebaia is a *persistent* spasm, and that of cryptopia an *intermittent* one. Thebaia holds the muscles with the most inflexible rigor, and the stiffened and motionless body may be held straight out by one of the extended hind legs. Cryptopia throws the whole of the voluntary muscular system into rapid and violent vibration. Thebaia descends upon the muscles like a stroke of lightning ; one minute the animal is tranquil in mind and body, the next he is thrown over, extended and stiffened, and, at the same time, suffocated by a prolonged iron-like grip of the chest. Cryptopia diffuses its influence gradually ; at first there is but a restless vivacity of the ordinary movements, a mere impulse to greater muscular activity ; after a while the impulse becomes stronger, but the animal is not yet deprived of control over his actions ; and now follows a remarkable struggle between voluntary and involuntary movement. As the influence of cryptopia increases, the former slowly gives way to the latter ; the battle, however, is severe, and the bodily and mental excitement intense, until the cryptopia obtains complete mastery, and then the helpless animal is thrown over on its side, vibrating with a violent,

intermittent spasm. The aëration of the blood, however, is not completely suspended, for the chest may still be said to pant under the influence of the spasm. The fit over, the animal is completely conquered and exhausted, and as the action of the alkaloid declines, and he slowly regains power over his movements, he now submits unresistingly to the influence of the cryptopia, and his body is affected with every variety of choreic movement. Thus, from first to last, cryptopia follows, so to speak, in the track of the ordinary movements, and ultimately excites them beyond the power of control; the primary chorea culminates in epilepsy, and the epileptic fits cease when the choreic movements decline in intensity.

Such is the main distinction between the convellent actions of thebaia and cryptopia on animals generally; but I must again go back to the mouse to show how this distinction is effaced. Thus, while cryptopia has no convellent action whatever on this animal, thebaia induces the vibratile spasm of cryptopia. Thebaia is to the mouse what cryptopia is to the dog, cat, or rabbit.

It now remains for us to consider the difference between the hypnotic and general effects of morphia and cryptopia. The sleep of cryptopia is as prolonged as that of morphia, but it is lighter and consequently more refreshing, and, as far as I have been able to ascertain, it is quite free from the illusions which so often attend sleep induced by morphia. But this is not the only advantage which cryptopia possesses over morphia. Cryptopia exercises no deranging influence over the vagus. The subcutaneous use of morphia in man is often followed by distressing sickness, and occasionally by alarming, not to say fatal, faintness; while in the dog, vomiting is the first and *invariable* consequence of its use. Such effects never, as far as I have seen, follow the use of cryptopia in any animal, whatever the dose may be. After the explanation given, and the want of similarity to the distressing effects of morphia, I cannot consider Obs. 8 as an exception to this statement. Cryptopia is therefore in many cases a pleasanter, and in all a safer, remedy than morphia given subcutaneously. As an anodyne I have reason to be well satisfied with cryptopia. I have employed it with a success equal to that obtainable by morphia, in several cases of severe neuralgia. Messrs. Smith prepare a soluble sulphate of the alkaloid, of which half a grain may be considered a medium

dose for a woman and one grain for a man, used subcutaneously. I prefer the acetate, however, as it is more soluble.

THEBAIA.

I know of no observation on the action of this alkaloid on man. It is assumed to have a simple tetanizing effect. I discovered in my earlier experiments that this was an imperfect view of its action, and that like all the other active constituents of opium, thebaia induces the two apparently opposite states of hypnosis and tetanus. In the lower animals the tetanizing action so greatly exceeds and disturbs the hypnotic effect, that the latter is overlooked. But even in these animals a marked degree of somnolency may be observed under the influence of moderate doses of the alkaloid. In man, however, and in medicinal doses, hypnosis, with contraction of the pupil, is the only effect to be observed. In nearly all of the following observations I have sat by the side of the patient during the action of the drug with the view of catching the first indications of convulsive action, but I have uniformly failed to witness the slightest tendency thereto. The largest dose given by the subcutaneous tissue was one and a half grain = six grains by the alimentary canal. The thebaia employed is identical in chemical and physical characters with that used in my former observations (op. cit., p. 179). The solution used was formed by dissolving thebaia in water by the aid of acetic acid, $\mathfrak{m}\text{xv}$ = one grain of the pure alkaloid. I have studied its action alone, and in combination with atropia, and in order to bring out its action upon man into stronger contrast, I shall preface my observations upon him by an illustration of the effects of a poisonous dose on the rabbit.

ON THE RABBIT.—*Obs. 12.*—Injected $\mathfrak{m}\text{xxx}$ of the solution = gr. ii thebaia, by two punctures beneath the skin of a healthy full grown rabbit, B. At the seventh minute the animal was aroused from a state of quietude by a few preliminary convulsive starts, and then thrown upon the side in strong opisthotonus spasms, the head being strongly retracted, and the fore legs stretched forwards and shaken with a fine rigid spasm. This continued with momentary interruptions, when the chest was released, and the respirations (84 and regular) could be

counted for a few seconds, until the twelfth minute, when the hind legs were thrown out in rigid spasm, and semen was ejected. The spasm only relaxed with death, at the seventeenth minute. The chest was opened six minutes afterwards. The lungs were of a salmon colour, and completely collapsed above and behind the heart. The great veins at the roots of the lungs, the cavæ, and the right heart, were enormously distended with venous blood. The right ventricle was motionless, the right auricle pulsating faintly but regularly 72. The left heart was contracted and motionless. On relieving the distension of the right auricle by dividing some small branches of veins converging to it, the contractions of this cavity became stronger, and were increased to 200 a minute. On puncturing the inferior cava just above the liver, a minute later, a stream of black blood spouted forth, and the right ventricle at first became flaccid, then, having contracted, began to beat regularly 84 times a minute, the auricular contractions under the influence of the free depletion being at the same time reduced to 70. These contractions of the right heart continued until the eighteenth minute after the death of the animal (the thirty-fifth after the injection of the poison), the pericardium lying open the whole of the time. The urinary and gall bladders were full; the urine was thick from amorphous deposit, and of a primrose-yellow colour.

Death was the direct result of simple cramp of the muscles of respiration sufficiently prolonged to exhaust the arterial blood of its oxygen.

ON MAN.—*Obs.* 13.—Samuel M—, æt. 50. Pulse 84, pupils one eighth, respiration 19-20. Accustomed to the subcutaneous use of the active principles of opium, occasionally given for the relief of severe facial neuralgia (see “*Old Veg. Neur.*,” *Obs.* 60). $\frac{m}{v}$ of the solution = one third grain of thebaïa were injected into the subcutaneous tissue of the arm. After fifteen minutes, somnolency. After thirty minutes continued somnolency; pulse 78, unchanged in volume and power; pupils one ninth; respiration 20-21, regular. After one hour, continued somnolency; pulse 78, a little fuller; pupils one ninth; respiration 20. After two and a half hours, somnolency had continued, and he had slept a quarter of an hour; but the effect was now passing off.

Pulse 78, decidedly fuller and stronger, and quite regular ; pupils dilated to their initial size ; mouth a little clammy ; felt quite comfortable during the action and continued to do so. Now walked home and went to bed, and slept soundly all night.

Obs. 14.—After an interval of four months, pulse 76 ; pupils one ninth, at a given distance from a gas light ; respiration 20. Injected \mathfrak{Mx} of the solution = two thirds of a grain. After thirty-five minutes, considerable somnolency, “ very heavy for sleep ; ” pulse 76, decidedly fuller ; pupils one tenth. After one hour and ten minutes, continued somnolency ; pulse 76, of increased volume and power ; pupils one tenth. After two hours, somnolency passed off ; pulse 68 of initial volume and power. Pupils nearly attained their initial dimension ; respiration 20. Now walked home, went to bed, slept soundly all night, and experienced decided somnolency next day.

Obs. 15.—After an interval of a week, the pulse being 72, small and weak, with an occasional intermission, right pupil one ninth, left one sixth,¹ injected \mathfrak{Mxv} = one grain. After thirty minutes, pulse 72, unchanged ; pupils one tenth ; respiration 20, regular ; great somnolency. After one hour, pulse 78 without intermission ; both pupils one tenth ; respiration 21. Had slept quarter of an hour, and was still very sleepy. After two hours, pulse 72, regular ; pupils returned to initial size ; respiration 18-19. Had been sleeping most of the time comfortably.

Obs. 16.—After an interval of six months, injected \mathfrak{Mxix} of the solution = one and a quarter grain, and he immediately walked home a distance of two miles, and went to bed. Somnolency came on ten minutes after the injection, and, after reaching home, he slept soundly through the remaining ten hours of the day, and the following night.

Obs. 17.—After an interval of five days, the pulse being 84 and small, the pupils one sixth, and the respiration 20, injected $\mathfrak{Mxxiiss}$ = one and a half grain of thebaia. After twenty minutes, pulse 76, unchanged in volume and power ; pupils one eighth ; respiration 21-22 ; great somnolency. After one hour and twenty minutes, pulse 76, unchanged ; pupils one eighth ; respiration

¹ The intermission of one or two beats a minute, and the inéquality of the pupils, were symptoms which commonly attended a paroxysm of neuralgia. This was confined to the right side of the face, and caused slobbering from the angle of the mouth, and hyperæsthesia of the affected part.

19-20. Somnolency continued, but a paroxysm of tic prevented sleep. Went home, slept soundly until next morning.

Obs. 18.—Mrs. T—, æt. 38, a weakly woman with impaired innervation of the lower extremities. Pulse 80; pupils one eighth; injected $\text{m} \times$ of the solution = two thirds of a grain thebaia into the subcutaneous tissue of the arm. After five minutes, began to feel a little giddy and stupid. After forty minutes, continued to feel stupid and a little sickish and faint, and could not walk without the support of the wall or furniture, having great difficulty in getting the weaker leg from the ground. Pulse and pupils unchanged. After one hour pulse, 78 and fuller; pupils not appreciably smaller. The effects were now passing off, and she was sitting in a chair talking to a friend. Shortly after she lay down and dozed comfortably for the rest of the afternoon.

Obs. 19.—Frederiek T—, æt. 22, rather lame from sciatica of eleven weeks' duration. Injected, on four separate occasions, $\frac{2}{3}$, 1, $1\frac{1}{3}$, and $1\frac{1}{2}$ grains of thebaia into the subcutaneous tissue of the thigh. A pleasant hypnotic effect followed each dose within ten minutes, increasing in intensity for the next hour, and then, as an irresistible influence, passing off; but, left quiet, the patient slept tranquilly for several hours afterwards. During sleep, or at the moment of awaking, the pupils were dilated, but on looking intently at a distant object they were decidedly contracted. The anodyne effect was such that the pain was relieved by the first injection, removed by the second, and has not returned since.

Obs. 20.—George H—, æt. 20, a delicate youth, took two grains of thebaia by the mouth every third day, six times. It caused a slight and transient giddiness, coming on after half an hour, and lasting about thirty minutes. After one dose there was a little somnolency, but this was attributed to over-eating.

CONCLUSIONS.—I have finished my previous observations on the action of the active principles of opium with these words:—"Since cryptopia throws one animal into convulsions, and acts as a pure hypnotic to another, it is not unreasonable to suppose that there may be nervous systems which are able, in like manner, to convert a large portion, if not all, of the impressions excited by thebaia into soporific effects."¹ The foregoing observations on man realize this supposition, and form a proper sup-

plement to what I have said respecting the connection between sleep and convulsion. The hypnotic action of thebaia on man is, as far as I have observed, free from all unpleasant effects (the symptoms mentioned in Obs. 18 would not have been experienced had the patient been recumbent and at rest). As a soporific $1\frac{1}{2}$ grain is about equal to $\frac{1}{4}$ of a grain of a salt of morphia.

The contracting effect on the pupil is, in most cases, much weaker than that of morphia; but it possesses an equally stimulating effect upon the pulse. The influence upon the respiratory movements, however, is the reverse of that of morphia, viz. stimulant. During the action of a quarter or half grain of acetate of morphia, the respirations in Samuel M—, usually decreased to 16 or 15 a minute.

THEBAIA AND ATROPIA COMBINED.

The following observations were made upon Samuel M—, the subject of Obs. 13 to .17. The solution of thebaia was that used in the previous Observations. The solution of atropia contained two grains of the sulphate in one ounce of water.

Obs. 21.—Pulse 72; pupils one eighth. Injected one sixth of a grain of thebaia and one forty-eighth of a grain of atropia sulphate by one puncture. Somnolency came on within four minutes. After one hour, pulse 102, fuller; pupils unchanged. Conjunctiva slightly injected; mouth and throat dry; continued very sleepy and comfortable. After two hours, had dozed since last date; mouth still dry; pulse 100; of good volume and power; pupils one seventh and one sixth, right and left respectively. The effect was now passing off.

Obs. 22.—Pulse 72; pupils one eighth. Injected one fourth of a grain of thebaia and one forty-eighth of a grain of atropia sulphate by one puncture. After twenty minutes, pulse 100, slight somnolency, and a little dryness of the mouth. After one hour, continued very dozy and comfortable. Pulse 100; pupils unchanged; mouth and throat very dry; respiration 20, regular. After two hours and twenty minutes, pulse 88, contracted, regular; respiration 20, regular; right pupil one seventh, the left a trifle larger. Throat and mouth very dry; was still sleepy, but the effect was now passing off.

Obs. 23.—Pulse 74; pupils one eighth; respiration 20. Injected one third of a grain of thebaia and one forty-eighth of a grain of atropia sulphate by one puncture. After twenty minutes, pulse 120, of good volume and power; pupils unchanged; respiration 23; dryness of throat, and somnolency. After one hour, pulse 120, contracted, but of fair power; pupils still unchanged; respiration 20, regular; had been dozing. After two hours, had continued very sleepy; pulse 110, contracted and regular; pupils one seventh and one sixth; respiration 20. Went home and slept comfortably all night, and experienced somnolency the next day.

Obs. 24.—Pulse 72; pupils one eighth; respiration 21. Injected half a grain of thebaia and one fortieth of a grain of atropia sulphate by one puncture. After fifty minutes, pulse 120; pupils unchanged; throat and mouth quite dry; great somnolency since five minutes after the injection. After two hours, pulse 98, soft, and of good volume; pupils one seventh and one sixth; respiration 19; mouth still dry; had slept comfortably for some time.

Obs. 25.—Pulse 80; pupils one eighth and one seventh respectively. Injected one grain of thebaia and one forty-eighth of a grain of atropia sulphate by one puncture. After one hour, pulse 120; pupils unchanged; mouth and throat very dry; great somnolency, and had slept for quarter of an hour. After two hours pulse 98; pupils one seventh and one sixth; continued somnolency, but the effect was now passing off. Went home and slept soundly all night.

From a comparison of these observations with those on thebaia alone, it will appear that atropia increases and prolongs the hypnotic action of thebaia. I have previously shown that it does not diminish its convellent action (*op. cit.*, p. 298). The counteracting effect of atropia upon the pupils, under the influence of thebaia and morphia, is about equal for equivalent doses. The stimulant effect of thebaia upon the respiratory movements is preserved under the combined action.

